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Metformin for the Prevention of Prediabetes Progression to Type 2 Diabetes: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: The aim of this meta-analysis was to explore the effectiveness of metformin in retarding the progression of pre-diabetes to type 2 diabetes (T2D).

Materials and methods: A web-based search was conducted using the Cochrane Library identifying ten citations for analysis. In the pre-analysis stage, outlier detection was carried out using funnel plots, culprit citations identified using Byjat plot and influence analysis. The meta-analysis was conducted using a random-effects model using relative-risk (RR) as the effect-size and prediction interval (PI) as the indicator of heterogeneity. The RR was calculated by comparing the metformin and the control arm [lifestyle modification (LSM)/placebo]. R studio (2022.07.1, Build 554) software was used for analysis.

Results: A total of 8869 patients with pre-diabetes were included in the meta-analysis, with 4328 patients in the metformin arm and 4541 in the control arm (LSM/placebo). There was a 22% RR reduction with metformin compared to LSM/placebo with a 95% CI of 0.71–0.86. No heterogeneity was detected in the summary effect size (PI: 0.69–0.88). Subgroup analysis using the dose of metformin (low versus high) did not influence the outcome (p = 0.39)

Conclusions: The addition of metformin to intensive LSM is an effective value addition in patients with pre-diabetes at high-risk of progression to T2D.

Keywords: pre-diabetes, type 2 diabetes, meta-analysis, metformin, LSM, placebo, systematic review

Introduction

Type 2 diabetes (T2D) is the forerunner of metabolic disease-associated morbidity and mortality. With a global prevalence of 6.1% translating into 529 million individuals, prevention of progression to T2D is the major focus of public health policies [1]. To compound the problem there has been a trend towards an increase in the prevalence of T2D in the younger age group [2]. This leads to a greater duration of exposure to hyperglycemia in an individual's lifetime leading to additional complications. There is a significantly higher risk for microvascular and macrovascular complications associated with early onset T2D. A 14-fold increase in myocardial infarction was reported when T2D was diagnosed in younger individuals (age < 45 years) [3].

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One of the strategies aiming at preventing this huge global disease burden is to identify the vast undetected population with pre-diabetes rapidly transitioning to T2D. Depending on the criteria used to define pre-diabetes [impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)], the 2021 global prevalence was estimated at 9.1% for IGT and 5.8% for IFG, with a projected increase to 10% and 6.5% respectively [4]. This translates into approximately 10,000 million individuals with pre-diabetes anticipated to join the T2D pool by the year 2045.

The predominant strategy used to prevent the transition from pre-diabetes to T2D has been lifestyle modification (LSM) aiming at weight loss and reduction in insulin resistance. However, achieving the required 5% weight loss from baseline for metabolic benefits is difficult to achieve and more importantly to sustain [5]. A mean weight loss of 6.5 kg from baseline in the diabetes prevention program (U.S. DPP) contrasts with the analysis of Davies et al., where the mean weight loss was a non-significant 0.27 kg [6, 7]. In view of this heterogeneity of outcomes certain medicines capable of inducing weight loss and improving insulin resistance (biguanides and thiazolidinediones) had been investigated. Metformin stands out as the most promising agent in view of its effect on weight and insulin resistance as well as a positive risk-benefit-cost effectiveness ratio [8].

The effectiveness of metformin in retarding the progress of pre-diabetes to overt T2D have been analyzed in a couple of systematic reviews [9, 10]. However, these studies did not take into account the heterogeneity of the data while performing the effect size analysis. This meta-analysis was undertaken to explore the effectiveness of metformin in preventing the pre-diabetes progression to T2D taking into account the inherent heterogeneity of the studies and re-analyzing the data having removed the significant outliers.

The PICO (Patient, Intervention, Comparison, Outcomes) search strategy was used to identify the suitable citations. Patient = Pre-diabetes; Intervention = Metformin; Comparison = LSM; Outcome = Progression to T2D

Materials and methods

This meta-analysis was conducted according to the recommendations of the PRISMA statement and registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 January 2024 with the INPLASY registration number: INPLASY202410050 [11].

Literature searches, search strategies, and eligibility criteria

The randomized prospective studies were identified through a thorough database search (Cochrane Library). The search was divided into two categories, (a) related to the intervention in question, and (b) related to the primary disease in question. The search terms were combined using the Booleans "OR" and "AND". The terms included (a) "Prediabetic state {MeSH}" OR "Glucose intolerance {MeSH}" OR "Impaired fasting glucose" OR "IFG" OR "Impaired glucose tolerance" OR "IGT", AND (b) "Metformin {MeSH}". All the variants of metformin including metformin hydrochloride and metformin HCL were included in the MeSH terminology. (Suppl. File 1) The primary filters included human subjects and trials, thereby excluding review articles and conference abstracts. Subsequently, duplicate citations were tracked and removed with the final step of screening being non-adherence to the pre-specified inclusion criteria (Fig. 1). The inclusion criteria included: Randomized prospective studies, studies reporting pre-diabetes in the standardized format including IFG and IGT, metformin as the primary intervention arm, LSM as the standard of therapy in the comparative arm, age above 18 years, and a minimum follow-up period of 6 weeks.

Data extraction including assessment of quality of studies

The identification and selection of the eligible citations was carried out using appropriate keywords. (Fig. 1) There was no restriction as far as the date of publication was concerned. The search was carried out using the English language as the medium for search. Any ambiguity or disagreement was resolved on a subsequent day by conducting another independent search and comparing it with the previous one. In the end, ten citations qualified for analysis. The quality of the selected citations was assessed using the Cochrane risk-of-bias algorithm, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome data, incomplete outcome data, selective reporting, and other biases (Suppl. File 2). Individual publication bias was assessed using funnel plots.

Patient approval and clearance from the ethical committee

In view of being a systematic review and meta-analysis, there was no direct handling of patients. In addition, effect size estimates that were already pub-

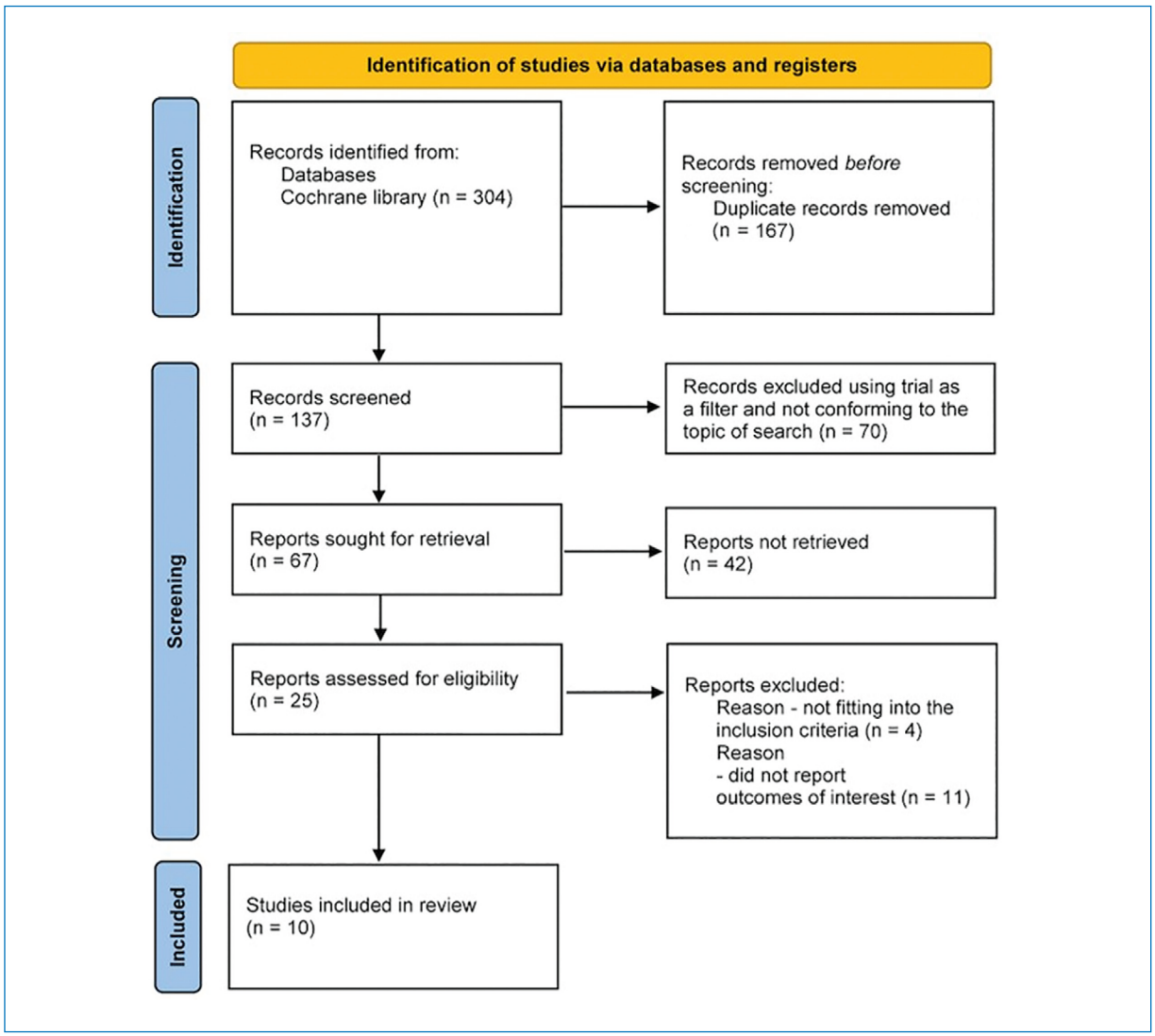

Figure 1. PRISMA Flow Chart of Identification, Screening, and Inclusion
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

lished and an open web-based domains were used to conduct the meta-analysis. As a result, there was no requirement for patient or ethical committee consent.

Statistical analysis

The R studio (2022.07.1, Build 554) software was used to conduct the statistical analysis. The codes used are provided in the Supplementary materials (Suppl. File 3).

The statistical analysis was planned in a stepwise manner.

Step 1: Pre meta-analysis; A publication bias assessment was conducted using the funnel plot and influence analysis. On detection of a significant influencer or funnel plot asymmetry using a p-value of ≤ 0.05 as the determinant of significance, a decision would be taken to either modify the effect size analysis using a Duvall's trim and fill method or using a leave-one-out sensitivity analysis by deleting the studies identified as gross outliers. In the absence of a significant heterogeneity, the former would be used.

Step 2: Meta-analysis; The meta-analysis was conducted using relative risk (RR) as the effect size. The effect size is reported as a 95% confidence interval (CI). In view of the random search and differing baseline characteristics of the citations, a random effects model was used for analysis.

The main focus was to assess the effect size and the heterogeneity of the outcome using the prediction interval (PI). The proportion of the heterogeneity of the observed effect size to the true population effect size would be determined using the I^2 statistics.

Step 3: Post meta-analysis; If a significant heterogeneity of the observed effect size is detected, a meta-regression analysis was planned to be conducted to identify any clinical or laboratory attribute explaining the heterogeneity. In the absence of heterogeneity, a subgroup analysis using the dose of metformin used and weight loss from baseline was planned.

Results

A total of 8869 patients with pre-diabetes were included in this meta-analysis, with 4,328 patients in the metformin arm and 4541 in the control arm. Impaired glucose tolerance (IGT) was used as the measure for pre-diabetes with the exception of Sussman et al., Weber et al., and Andreadis et al. Both IGT and IFG were included as a criteria for pre-diabetes in Sussman et al. whereas IFG, IGT, and the combination of IFG and IGT were used in Weber et al. and Andreadis et al. In all the studies conventional lifestyle modifications was used as control whereas a few (O'Brien et al., Li et al., and Sussman et al.) had a decoy tablet as placebo. The dose of metformin varied across the trials ranging from 500 mg per day to 1700 mg per day. The mean duration of follow-up ranged between 12–36 months (Tab. 1).

The quality of the studies was assessed using the Cochrane risk of bias algorithm. There were some concerns related to bias due to missing outcomes in the studies by Iqbal et al and Li et al., related to bias in the measurement of outcomes in Sussman et al., Iqbal et al., and Andreadis et al., and related to bias in the selection of reported results in Ratner et al. Overall, there were no major concerns related to bias in the studies selected for meta-analysis.

The selection of the final set of studies for the meta-analysis was made based on funnel plot asymmetry and influence analysis. The summary of the model created using all the ten citations resulted in significant heterogeneity ($p = 0.001$, $Q = 37.6$, $df = 9$) and funnel plot asymmetry ($p = 0.02$). (Suppl. File 4). The adverse influencer was identified using the Baujat plot and influence analysis. (Suppl. File 5 A and B) The influence on the mean effect size was confirmed using a leave-one-out sensitivity analysis (Suppl. File 5 C). Iqbal et al. contributed to significant heterogeneity and funnel plot asymmetry. The whole process was repeated excluding Iqbal et al. There was a significant impact on heterogeneity and funnel plot asymmetry (qualitative) by Andreadis et al. (Suppl. Files 6 and 7). As a result the final analysis was carried out using 8 citations. This made the process of summary effect size estimation extremely conservative.

Primary outcome

There was a 22% relative risk reduction in the progression from pre-diabetes to T2D with the use of metformin compared to LSM and/or placebo (95% CI 0.71–0.86). The result was robust in view of the fact, that there was no significant heterogeneity in the summary effect size (prediction interval 0.69–0.88) (Fig. 2). In view of the absence of significant heterogeneity, a meta-regression analysis was not done.

The secondary outcome is the subgroup analysis based on the dose of metformin. The dose of metformin used in the studies were divided into low dose ($\leq$ 1000 mg/day) and high dose ($>$ 1000 mg/day). There was no difference in the RR reduction of progression to T2D with metformin compared to lifestyle intervention based on the dosage used (p-value for interaction = 0.39). (Fig. 3)

Discussion

The huge global population of individuals with pre-diabetes with a conversion rate of approximately 25% represents the tip of the "sugary" iceberg, about to explode on the face of the public health care system. With an annual progression rate of 3.5–7.0%, pre-diabetes should indeed be the primary focus of metabolic disease preventive strategy [22]. The risk of progression is higher in those with combined IFG and IGT. The actual figures could be much higher since, glycated hemoglobin (HbA1c) based assessment was not included in most of these analyses. Individuals with prediabetes in the HbA1c range of 6.1–6.4% have an annual conversion rate of 10% [23].

These alarming numbers indicate the need to implement management strategies aimed at prevention of progression of pre-diabetes to overt T2D. Lifestyle management aimed at a 5% weight loss from baseline is considered as the primary management strategy, especially in those who are overweight, obese, or have other manifestations of insulin resistance [5]. One school of thought advocates against the use of medications in pre-diabetes in view of its low correlation with microvascular complications [24]. However, with only 20% success rate in maintaining weight loss in the long run, this argument does not hold ground [25]. There is a need to consider medications especially metformin in conjunction with intensive LSM, especially in those with a high risk of progressing to T2D.

Most of the individual prospective studies assessing the effectiveness of metformin in the progression of pre-diabetes to T2D had their effect size in the right direction. The exceptions were the diabetes prevention program (DPP), Ratner et al., and Li et al. [13, 14, 19]. In view of the differing baseline populations, the choice of

Table 1. Baseline Characteristics of the Studies Included for Meta-Analysis

Authors	Year	Control	Intervention	Intervention/ /Control (n)	Pre-diabetes type	Duration of follow-up (months)	Type of study	Country
Iqbal et al. [12]	2012	Lifestyle modification	Metformin 500 mg BID	82/85	IGT	18	Randomized controlled clinical trial	Pakistan
Orchard et al. [13]	2005	Lifestyle modification	Metformin 850 mg BID	503/490	IGT	28.4	Randomized controlled clinical trial	United States
Li et al. [14]	1999	Placebo	Metformin 250 mg TID	33/37	IGT	12	Randomized controlled clinical trial	China
Ramchandran et al. [15]	2006	Lifestyle modification	Metformin 250 mg BID	128/133	IGT	36	Prospective randomized, controlled clinical trial	India
O'Brien et al. [16]	2015	Placebo	Metformin 850 mg BID	983/967	IGT	33.6	Randomized controlled clinical trial	United States
Sussman et al. [17]	2015	Placebo	Metformin 850 mg BID	1027/1030	IFG + IGT	36	Post hoc analysis	United States
Weber et al. [18]	2016	Lifestyle modification	Metformin 500 mg BID	283/293	IFG (30.2%), IGT (29.7%), and IFG + IGT (40.1%)	30	Randomized controlled translation trial	India
Ratner et al. [19]	2008	Lifestyle modification	Metformin (dose not mentioned)	111/122	IGT	36	Randomized controlled clinical trial	United States
Knowler et al. [20]	2002	Lifestyle modification	Metformin 850 mg BID	1073/1087	IGT	36	Randomized controlled clinical trial	United States
Andreadis et al. [21]	2008	Lifestyle modification	Metformin 850 mg OD	92/274	IFG, IGT, and combined IFG + IGT	12	Prospective study	Greece

BID — twice daily; IFG — impaired fasting glucose; IGT — impaired glucose tolerance; OD — once daily; TID — thrice daily

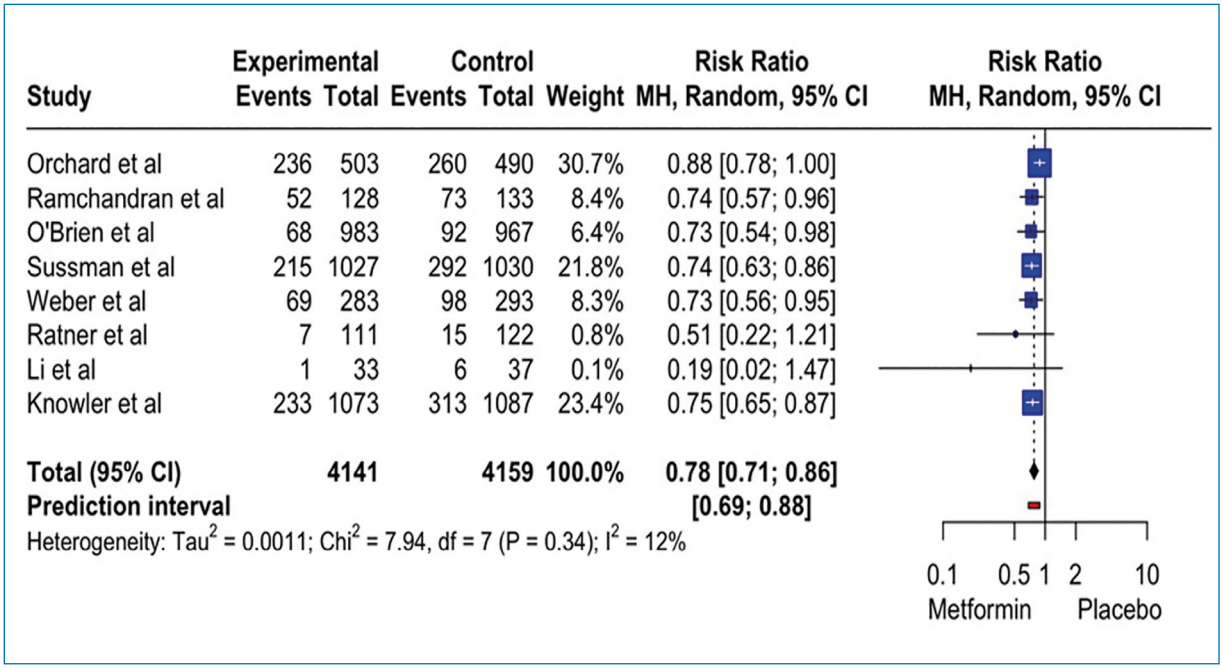

Figure 2. Meta-Analysis of 8 Citations Comparing the Efficacy of Metformin with Lifestyle Modification in Prevention of Progression of Pre-Diabetes to T2D
CI — confidence interval; MH — Mantel-Haenszel statistic; T2D — type 2 diabetes

the biochemical parameter to identify pre-diabetes, and background risk factors a couple of meta-analyses were conducted to assess the efficacy of metformin by pooling all these data. Lily et al. conducted a meta-analysis with 3 studies and documented a 35% relative risk reduction with metformin [26]. However, this manuscript was constrained by the small number of studies as well as the fixed-effect model used for the meta-analysis. The latter is not ideal to check for heterogeneity of the summary effect size as well as prone to inflation of the mean effect size. Another meta-analysis by Patel et al. with 17 studies documented a 42% relative risk reduction with medications [27]. However, this cannot be considered as an assessment of metformin in the strictest sense due to the inclusion of studies like Zinmann et al. where the intervention arm had both metformin and rosiglitazone [28]. In addition, there was a significant heterogeneity associated with the summary effect size making it difficult to attribute the benefits solely to the intervention. The effectiveness of the interventions could be related to the baseline body mass index (BMI). In the study by Knowler et al., it was documented that prevention of prediabetes with metformin was greatest in those with a higher baseline BMI [20].

In view of these limitations, this meta-analysis was conducted with the aim to assess metformin (exclusively) in pre-diabetes using the random-effects model aiming at identifying heterogeneity if any, and trying to explore the clinical and laboratory attributes contributing to it. The studies by Iqbal et al. and Andreadis et al. were excluded from the analysis in view of the "small study effect" in the funnel plot analysis and "heterogeneity assessment "with the Byjat plot and influence analysis. The meta-analysis with eight selected citations resulted in a 22% relative risk reduction with metformin compared to LSM or placebo, with a 95% confidence interval of 0.71–0.86. There was no heterogeneity in the summary effect size as evidenced by the prediction interval (0.69–0.88). The detection of potential outliers early on in this meta-analysis was probably the reason we got a more conservative summary effect size in comparison to the earlier meta-analyses. In the absence of heterogeneity, we could attribute the positive impact on progression to T2D on metformin and hence a meta-regression analysis was not needed. Subgroup analysis using the dose of metformin (low versus high) did not have any impact on the final outcome (p-value for heterogeneity = 0.39).

Limitations and strengths

This meta-analysis had a few limitations. The analysis was conducted using summary data published in journals and hence did not include individual patient data. In addition, the baseline definition of pre-diabetes was not uniform. The risk of progression to T2D is highest with IGT and IFG, followed by IGT, and then IFG.

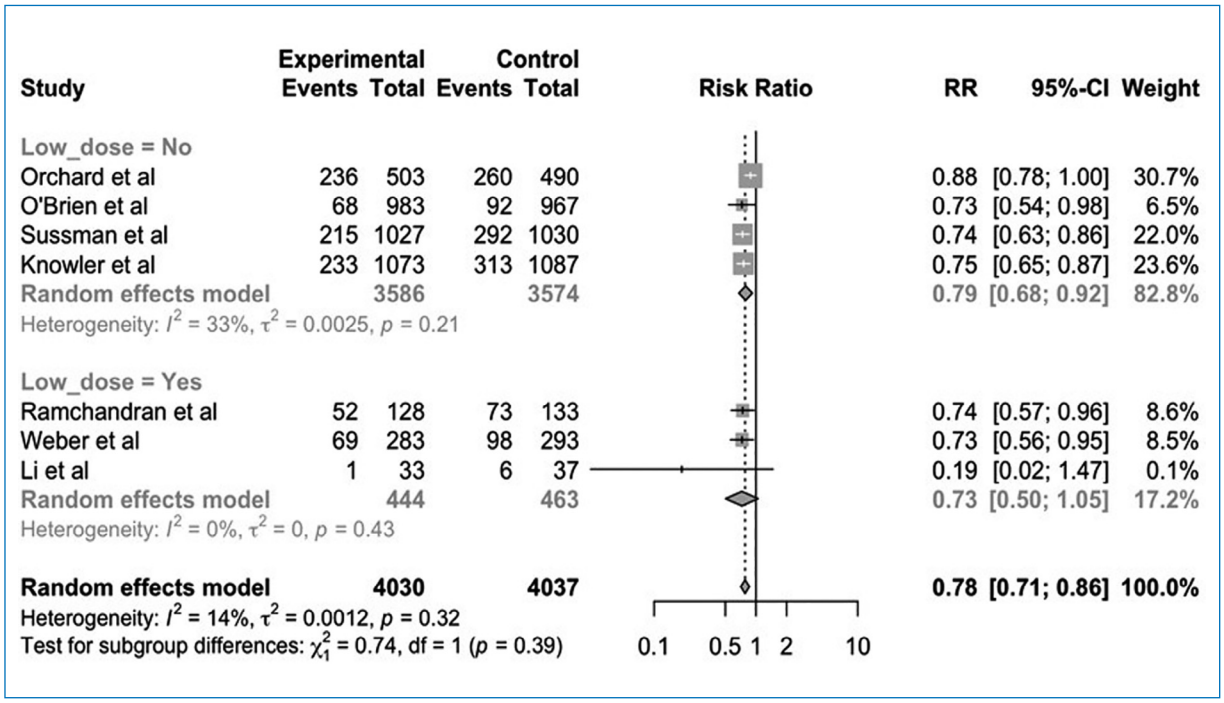

Figure 3. Subgroup Analysis Exploring the Impact of Metformin Versus Lifestyle Modification on the Prevention of Progression to T2D from Pre-Diabetes Depending upon the Dose of Metformin
CI — confidence interval; T2D — type 2 diabetes

These differing definitions could have had an influence on the final outcomes. Influential parameters, for example body mass index, weight, waist circumference, markers of insulin resistance, etc., were not uniformly reported in these citations making it impossible to conduct an explanatory analysis.

The main strength of this meta-analysis was the inclusion of the largest number of studies till date to compute a summary effect size. In addition, all the prerequisite safeguards were taken to avoid inflation of the effect size and inducing heterogeneity. The exclusion of any active intervention in the control arm made the assessment of metformin more focused and accurate as evidenced by the precision interval.

Conclusions

Pre-diabetes is a ticking "time-bomb" in the public health domain. Lifestyle modification remains the cornerstone for the management of pre-diabetes. In selected population with high risk for progression to T2D, metformin offers a value addition. This meta-analysis demonstrates the effective risk reduction that metformin can offer to patients with prediabetes at high risk for progression to T2D.

Article information

Supplementary materials

The Supplementary materials for this article can be found at https://journals.viamedica.pl/clinical_diabetology/article/view/99821

Authors' contribution

Dr. SG is involved in conceptualizing, designing manuscript writing, and approval. Dr. ST and Dr. SP are involved in literature research, data screening, selection and data extraction, manuscript review, and journal formatting. Dr. KS is involved in conceptualizing, design, review and approval of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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